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EXAMINER	
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ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/692,523	RICHON, VICTORIA M.	
	Examiner	Art Unit	
	JAMES D. ANDERSON	1614	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 December 2007 and 08 January 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,12-15,157 and 179* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,12-15,157 and 179* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/13/2005 and 1/8/2008*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 1, 12-15, 157 and 179 are presented for examination

Applicants' amendment filed 12/20/2007 has been received and entered into the application. Accordingly, claims 1 and 157 have been amended, claim 179 has been added, and claims 2-3 have been cancelled.

Applicants' arguments have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous Office Actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant application.

Information Disclosure Statement

Receipt is acknowledged of the Information Disclosure Statement filed 1/8/2008. The Examiner has considered the references cited therein to the extent that each is a proper citation. Please see the attached USPTO Form 1449.

In addition, the IDS filed 9/13/2005 was scanned as a Miscellaneous Incoming Letter and does not appear to have been considered. Accordingly, the Examiner has herein considered the IDS filed 9/13/2005. Please see the attached USPTO Form 1449.

Response to Arguments

Applicant's arguments filed 12/20/2007 have been fully considered but they are not persuasive. In traversing the rejection of claims 1-3, 12-15, and 157 (now 1, 12-15, 157, and 179) as being obvious over the cited references, Applicants present the following arguments.

In the previous Office Action, the Examiner indicated that no support was found in Provisional Application No. 60/361,759, filed March 4, 2002, for the treatment of "leukemia" as recited in the claims under examination. In response, Applicants have amended the claims to recite the treatment of acute leukemia, support for which they assert is found at page 11, line 13 of the '759 application. As such, Applicants argue that the instant claims are entitled to a priority date of March 4, 2002, which predates Curley *et al.* (Published May 2002) as applied in the present rejections. However, the recitation of "acute leukemia" in the '759 application is directed to a very specific patient population (*i.e.*, patients who tolerated the drug without toxicity and there was a positive response). These limitations are not present in the claims as amended. Further, with respect to acute leukemia, the '759 application teaches that continuous infusion "would seem to be indicated" for such patients. However, the instant claims are directed to oral administration of a specific dose (400 once daily). Accordingly, the Examiner is not persuaded that the '759 application provides support for the instantly claimed treatment of acute leukemia comprising orally administering SAHA in a dose of 400 mg once daily. As Applicants' arguments are directed solely to Curley *et al.* not being available as prior art, the rejections of record are maintained and reiterated below for the reasons discussed *supra*.

With respect to the 35 U.S.C. 103 rejection over Vrana *et al.* and Amin *et al.* in view of Breslow *et al.*, Applicants argue that the combination of Vrana *et al.* and Amin *et al.* is deficient because they fail to teach or suggest the treatment of acute leukemia in patients by oral administration of a total daily dose of 400 mg of SAHA. Applicants assert that Breslow *et al.* fail to cure the deficiencies of Vrana *et al.* and Amin *et al.* because Breslow *et al.* is also silent regarding treating acute leukemia in patients by orally administering SAHA at a total daily dose

of 400 mg. However, as discussed in the previous Office Action and reiterated below, Vrana *et al.* and Amin *et al.* motivate one skilled in the art to use SAHA to treat leukemia, including the instantly claimed acute leukemia, wherein Vrana *et al.* teach that SAHA induces apoptosis in U937 human leukemia cells and suggest that, given evidence of activity of hybrid polar compounds such as HMBA in some hematologic malignancies, as well as the considerably greater potency of SAHA as an inducer of cell differentiation and apoptosis (in murine leukemia cells), "further efforts to elucidate the molecular determinants of action of SAHA and related agents could have therapeutic implications". Amin *et al.* teach that inhibition of histone deacetylase is emerging as a promising therapeutic tool in malignant diseases including acute myelogenous leukemia and demonstrates that histone deacetylase inhibitors (including the instantly claimed SAHA) induce caspase-dependent apoptosis in acute promyelocytic leukemia and the authors conclude that "apoptosis induced by HDAC inhibitors in APL could provide an effective strategy for treatment of patients with *t*(15;17)". As such, Vrana *et al.* and Amin *et al.* clearly motivate one skilled in the art to use SAHA in the treatment of acute leukemias. Breslow *et al.* provide the skilled artisan with the means to administer SAHA orally in the dose instantly claimed, wherein they teach methods of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells. The invention also provides a method of treating patients having tumors comprising administering to said patient a compound of the invention, including the instantly claimed SAHA. Administration of the disclosed compounds may be effected orally or parenterally. While the combination of Vrana *et al.*, Amin *et al.*, and Breslow *et al.* does not explicitly teach a total daily dose of 400 mg, optimizing the dosing and administration schedule of therapeutic agents is well within the purview of the skilled

artisan and one skilled in the art would be motivated to adjust dosing to elicit an optimal treatment regimen while minimizing toxicity. As such, and in the absence of a showing of unexpected results commensurate in scope with the claims, Applicants' recited dose of 400 mg is not seen as inventive over the prior art references.

Priority

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. § 119(e) or under 35 U.S.C. § 120, 121, or 365(c) is acknowledged. Upon further consideration, Applicant has not complied with one or more conditions for receiving the benefit of an earlier filing date under 35 U.S.C. § 119(e) and 35 U.S.C. § 120 as follows:

The later-filed application must be an application for a patent for an invention, which is also disclosed, in the prior application (the parent or original nonprovisional application or provisional application). The disclosure of the invention in the parent application and in the later-filed application must be sufficient to comply with the requirements of the first paragraph of 35 U.S.C. 112. See *Transco Products, Inc. v. Performance Contracting, Inc.*, 38 F.3d 551, 32 USPQ2d 1077 (Fed. Cir. 1994).

The disclosure of the prior-filed application, Application No. 60/361,759 (filed 3/4/2002), fails to provide adequate support or enablement in the manner provided by the first paragraph of 35 U.S.C. § 112 for one or more claims of this application.

The instantly claimed invention is drawn to the treatment of acute leukemia in a subject comprising orally administering a once daily dose of 400 mg of the histone deacetylase inhibitor, SAHA.

The disclosure of U.S. Provisional Application No. 60/361,759, filed 3/4/2002, is drawn to the use of histone deacetylase inhibitors, including the instantly claimed SAHA (page 7), for inducing terminal differentiation of neoplastic cells (page 9). The invention disclosed in the '759 application also provides a method of treating a patient "having a tumor" comprising administering an effective amount of any of the compounds disclosed therein (page 10). The term tumor, as used in the '759 application, is defined as any cancer caused by the proliferation of neoplastic cells, "such as lung cancer, acute lymphoid myeloma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, bladder melanoma, renal carcinoma, breast carcinoma, prostate carcinoma, ovarian carcinoma, or colorectal carcinoma" (page 11). The treatment of leukemia is not disclosed or supported by the '759 application. The recitation of "acute leukemia" in the '759 application is directed to a very specific patient population (*i.e.*, patients who tolerated the drug without toxicity and there was a positive response). These limitations are not present in the claims as amended. Further, with respect to acute leukemia, the '759 application teaches that continuous infusion "would seem to be indicated" for such patients. However, the instant claims are directed to oral administration of a specific dose (400 once daily).

In light of the above, the instantly claimed methods of treating acute leukemia in a subject comprising orally administering a once daily dose of 400 mg of the histone deacetylase inhibitor, SAHA, are afforded a priority date of 10/24/2003, the filing date of the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(e), (f) or (g) prior art under 35 U.S.C. § 103(a).

Claims 1, 157, and 179 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Vrana *et al.*** (Oncogene, 1999, vol. 18, pages 7016-7025) and **Amin *et al.*** (British Journal of Haematology, 2001, Vol. 115, pages 287-297) in view of **Curley *et al.*** (Proceedings of ASCO, 2002, vol. 21, page 6b, entry 1831)[1].

The instant claims recite the treatment of acute leukemia in a subject comprising orally administering a once daily dose of 400 mg of the histone deacetylase inhibitor, SAHA.

Vrana *et al.* teach that SAHA induces apoptosis in U937 human leukemia cells (Abstract). SAHA is second-generation hybrid polar compound recently shown to be a potent

[1] Curley *et al.* qualifies as prior art under 35 U.S.C. § 102(a) because the instantly claimed method of treating leukemia is not supported by Applicants' prior-filed Non-Provisional application (filed 3/4/2002).

inducer of differentiation in murine erythroleukemia (MEL) cells (page 7016). Another prototypical compound of the same class as SAHA, HMBA, has exhibited clinical activity in patients with myelodysplastic syndromes and leukemia (*id.*, right column). In MEL cells, SAHA has been shown to be 2,000-fold more potent than HMBA in promoting differentiation (*id.*). Further, treatment of MEL cells with SAHA (but not HMBA) has been found to inhibit histone deacetylases, enzymes implicated in the transcriptional regulation of genes involved in cellular maturation (*id.*). Vrana *et al.* show that when administered above threshold concentrations, SAHA "potently induces loss of U937 [leukemia cells of human origin] cell mitochondrial membrane potential and apoptosis" (page 7016 bridging page 7017). The authors conclude that the present findings demonstrate that SAHA, a hybrid polar compound and histone deacetylase inhibitor ~2000-fold more active than HMBA as an inducer of MEL cell maturation, potently triggers apoptosis in human myeloid leukemia cells (page 7023, left column). Finally, the authors suggest that, given evidence of activity of hybrid polar compounds such as HMBA in some hematologic malignancies, as well as the considerably greater potency of SAHA as an inducer of cell differentiation and apoptosis (in murine leukemia cells), "further efforts to elucidate the molecular determinants of action of SAHA and related agents could have therapeutic implications" (page 7023, right column). Vrana *et al.* do not expressly disclose the treatment of leukemia in a subject using the instantly claimed oral dose of 400 mg.

Amin *et al.* teach that inhibition of histone deacetylase is emerging as a promising therapeutic tool in malignant diseases including acute myelogenous leukemia (page 287, right column). The present study demonstrates that histone deacetylase inhibitors (including the instantly claimed SAHA) induce caspase-dependent apoptosis in acute promyelocytic leukemia

and the authors conclude that "apoptosis induced by HDAC inhibitors in APL could provide an effective strategy for treatment of patients with *t*(15;17)" (Abstract; Figure 5; page 294, right column; page 296).

Neither Vrana *et al.* nor Amin *et al.* teach oral administration of SAHA in a dose of 400 mg.

However, Curley *et al.* teach that the histone deacetylase inhibitor, SAHA, has good bioavailability and biologic activity when orally administered. A new oral formulation of SAHA was escalated in patients from 200 mg daily, 400 mg daily, 400 mg BID (twice a day), 800 mg BID, 1200 mg BID, 1600 mg BID, and 2000 mg BID (Abstract). Accordingly, the authors conclude that oral administration of SAHA is feasible and does have biologic activity (*id.*).

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Scope and Content of the Prior Art

In the instant case, Vrana *et al.* and Amin *et al.* teach the instantly claimed SAHA, demonstrate that it induces apoptosis in a human leukemia cell lines *in vitro*, and teach that SAHA is more potent that a related compound that has exhibited clinical activity in patients with leukemia. Curley *et al.* teach that oral administration of SAHA, in doses ranging from 200 daily to 2000 mg twice a day, is biologically active and exhibits good bioavailability.

Differences Between Prior Art and Claims

The instantly claimed methods appear to differ from the methods taught in Vrana *et al.* and Amin *et al.* in that the treatment of leukemia in a subject in the oral doses instantly claimed are not explicitly taught in the references. However, Curley *et al.* suggest and motivate the instantly claimed oral doses of SAHA and further teach that such doses have biological activity.

Level of Ordinary Skill in the Art

A person having ordinary skill in the art at the time of the present invention would generally be an oncologist with several years of experience in drug administration.

Objective Evidence and Motivation

In light of the above findings relating to the three *Graham* factors, the skilled artisan would have been motivated to administer the histone deacetylase inhibitor, SAHA, to treat acute leukemia in subjects in the oral dose instantly claimed. With respect to the instantly claimed oral administration, Curley *et al.* suggest and motivate the instantly claimed oral doses of SAHA and further teach that such doses have biological activity. Thus, one skilled in the art would reasonably expect that SAHA, as taught in Vrana *et al.* and Amin *et al.* as a potent inducer of apoptosis in human leukemia cell lines, could be effectively orally administered in the instantly claimed dose.

Finally, it is well established in the art that researchers routinely use *in vitro* assays in order to establish efficacy of potential anticancer agents. Such assays are generally considered by those skilled in the art to be reasonably predictive of *in vivo* efficacy. *In vitro* testing permits

an investigator to establish the rank order of compounds with respect to the particular pharmacological activity, *i.e.*, to determine the relative potency of the compounds. Compounds having the highest ranking or potency are then selected for further testing *in vivo*. Presumably this is the accepted practice in the pharmaceutical industry as *in vitro* testing, in general, is relatively less complex, less time consuming, and less expensive than *in vivo* testing. Moreover, *in vitro* results with respect to a particular pharmacological activity are generally predictive of *in vivo* test results, *i.e.*, there is a reasonable correlation therebetween. Were this not so, the testing procedures of the pharmaceutical industry would not be as they are. While the Examiner concedes that there is not an invariable exact correlation between *in vitro* test results and *in vivo* test results, successful *in vitro* testing for a particular pharmacological activity establishes a significant probability that *in vivo* testing for this particular pharmacological activity will be successful. For example, the court held in *Cross et al. v. Iizuka et al.*, 224 USPQ 739 (Fed. Cir. 1985) that:

> "...*in vivo* testing is but an intermediate link in a screening chain which may eventually lead to the use of the drug as a therapeutic agent in humans. We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further *in vivo* testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility". Cf. *Nelson,* 626 F.2d at 856, 206 USPQ at 883.

While the issue in Cross *et al. v.* Iizuka *et al.* was directed to the utility provision of 35 U.S.C. § 101, the fact remains that *in vitro* testing is an established practice in the art of drug discovery that establishes both the motivation to treat a human patient as well as establishing a reasonable expectation of success.

Thus, it would have been *prima facie* obvious to one of ordinary skill in the art to treat leukemia by orally administering SAHA in the dose instantly claimed. It is the Examiner's position that Vrana *et al.* and Amin *et al.* motivate the treatment of leukemias by administering compounds such as SAHA. Oral administration of the compounds of the invention is also suggested as an effective administration route for SAHA as evidenced by Curley *et al.* Although the administration disclosed in Curley *et al.* was not for the treatment of leukemia, one skilled in the art would have been motivated to use the oral doses disclosed in Curley *et al.* to treat leukemias as suggested and motivated by Vrana *et al.* and Amin *et al.* The combined references clearly teach that: 1) SAHA may be effective in the treatment of leukemias (Vrana *et al.* and Amin *et al.*); 2) SAHA is a histone deacetylase inhibitor that is orally bioavailable and biologically active in the doses instantly claimed (Curley *et al.*); and 3) compounds similar to SAHA been demonstrated to be effective in the clinical treatment of leukemia (Vrana *et al*). With respect to "continuous administration" as recited in newly added claim 179, it is well within the purview of the skilled artisan to optimize the administration schedule of therapeutic agents. In fact, such modification and optimization of administration schedules of carried out on a routine basis in the art as evidenced by Curley *et al.*

Thus, the skilled artisan would have been imbued with at least a reasonable expectation that acute leukemia could be effectively treated by oral administration of SAHA to patients having acute leukemias.

Claims 12-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Vrana *et al.*** (Oncogene, 1999, vol. 18, pages 7016-7025), **Amin *et al.*** (British Journal of Haematology, 2001, Vol. 115, pages 287-297), and **Curley *et al.*** (Proceedings of ASCO, 2002, vol. 21, page 6b, entry 1831) as applied to claims 1, 157, and 179 above, and further in view of **Grant *et al.*** (Pub. No. 2005/0004007 A1, based on the earlier U.S. filing date) and **Kabadi** (EP 0 547 000 A1).

Claims 12-15 of the instant application recite methods of orally administering a composition comprising SAHA, wherein the composition is contained in gelatin capsules and further comprises microcrystalline cellulose, sodium croscarmellose, and magnesium stearate.

Scope and Content of the Prior Art

Grant *et al.* teach oral administration (page 4, [0036]) of agents, which include the instantly claimed SAHA (page 5, [0039]). The reference also teaches soft or hard gelatin capsules for administration purposes (page 5, line 6). Grant *et al.* do not teach microcrystalline cellulose, croscarmellose sodium, and magnesium stearate as components of the pharmaceutical compositions disclosed therein.

However, Kabadi teaches a pharmaceutical composition for oral administration comprising fluvastatin (active ingredient), microcrystalline cellulose, croscarmellose sodium, and magnesium stearate (page 9, Example 4).

Differences Between Prior Art and Claims

The prior art does not expressly teach a composition for oral administration comprising SAHA, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

Objective Evidence and Motivation

Microcrystalline cellulose, croscarmellose sodium, and magnesium stearate are commonly used excipients in pharmaceutical compositions that are to be administered orally as evidenced by Kabadi. The above additives are well known to those skilled in the art as physiologically inactive ingredients that are added as a binder, disintegrant, and lubricant, respectively. One of ordinary skill in the art would find it obvious to use the claimed physiologically inactive ingredients taught in Kabadi in a pharmaceutical composition comprising SAHA for oral administration.

Claims 1, 157, and 179 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Vrana *et al.*** (Oncogene, 1999, vol. 18, pages 7016-7025) and **Amin *et al.*** (British Journal of Haematology, 2001, Vol. 115, pages 287-297) in view of **Breslow *et al.*** (U.S. Patent No. 6,087,367; Issued Jul. 11, 2000).

Vrana *et al.* and Amin *et al.* disclose as discussed *supra*. The references do not teach treating "subjects" with acute leukemia by oral administration of SAHA.

However, Breslow *et al.* teach methods of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells (Abstract). The invention also provides a method of treating patients having tumors comprising administering to said patient a

compound of the invention (Abstract; col. 2, lines 44-47; col. 11, line 60 to col. 12, line 17). The compounds disclosed in Breslow *et al.* include the instantly claimed SAHA (col. 7, lines 1-42; col. 26, line 55 to col. 27, line 24; Table 1, Compound 3). Administration of the disclosed compounds may be effected orally or parenterally (col. 11, line 67 to col. 12, line 1). Breslow *et al.* do not expressly disclose the instantly claimed oral dose of SAHA or the specific treatment hematological malignancies such as leukemia.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Scope and Content of the Prior Art

In the instant case, Vrana *et al.* and Amin *et al.* motivate the use of SAHA to treat leukemias as discussed *supra* and Breslow *et al.* suggest that SAHA may be orally administered. Further, Breslow *et al.* suggest that the compounds of the invention, including the instantly claimed SAHA, are useful in methods of inducing terminal differentiation of neoplastic cells.

Differences Between Prior Art and Claims

The instantly claimed methods appear to differ from the methods taught in Vrana *et al.* and Amin *et al.* in that oral administration of SAHA to a subject is not explicitly taught. The

instantly claimed methods differ from Breslow *et al*. in that the specific treatment of leukemia comprising a once daily 400 mg oral dose of SAHA is not explicitly taught in the reference.

Level of Ordinary Skill in the Art

A person having ordinary skill in the art at the time of the present invention would generally be a physician with several years of experience in drug administration.

Objective Evidence and Motivation

In light of the above findings relating to the three *Graham* factors, the skilled artisan would have been motivated to administer the histone deacetylase inhibitor, SAHA, to treat leukemia in the oral dose instantly claimed. With respect to the treatment of acute leukemia, the Examiner refers to the discussion *supra*. With respect to the instantly claimed 400 mg once daily oral administration of SAHA and "continuous administration" as recited in claim 179, optimization of patient dosing is more than routine in the art of drug administration. For example, once a candidate drug has been chosen through *in vitro* and *in vivo* screening, Phase I clinical trials are conducted in order to develop the best dosing regimen for Phase II trials. As such, the instantly claimed 400 mg once daily dose of SAHA and "continuous administration" would have been *prima facie* obvious because such a dosing regimen could readily be elucidated through routine experimentation and optimization.

Claims 12-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over **Vrana *et al.***, **Amin *et al.***, and **Breslow *et al.*** as applied to claims 1, 157, and 179 above, and further in view of **Grant *et al.*** (Pub. No. 2005/0004007 A1, based on the earlier U.S. filing date) and **Kabadi** (EP 0 547 000 A1).

Claims 12-15 of the instant application recite methods of orally administering a composition comprising SAHA, wherein the composition is contained in gelatin capsules and further comprises microcrystalline cellulose, sodium croscarmellose, and magnesium stearate.

Scope and Content of the Prior Art

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However, Kabadi teaches a pharmaceutical composition for oral administration comprising fluvastatin (active ingredient), microcrystalline cellulose, croscarmellose sodium, and magnesium stearate (page 9, Example 4).

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The prior art does not expressly teach a composition for oral administration comprising SAHA, microcrystalline cellulose, croscarmellose sodium, and magnesium stearate.

Objective Evidence and Motivation

Microcrystalline cellulose, croscarmellose sodium, and magnesium stearate are commonly used excipients in pharmaceutical compositions that are to be administered orally as evidenced by Kabadi. The above additives are well known to those skilled in the art as physiologically inactive ingredients that are added as a binder, disintegrant, and lubricant, respectively. One of ordinary skill in the art would find it obvious to use the claimed physiologically inactive ingredients taught in Kabadi in a pharmaceutical composition comprising SAHA for oral administration.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JAMES D. ANDERSON whose telephone number is (571)272-9038. The examiner can normally be reached on MON-FRI 9:00 am - 5:00 pm EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ardin Marschel can be reached on 571-272-0718. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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